Risk factors for schizophrenia. Follow-up data from the Northern Finland 1966 Birth Cohort Study

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This paper updates single risk factors identified by the Northern Finland 1966 Birth Cohort Study up to the end of year 2001 or age 34. Impaired performance (e.g., delayed motor or intellectual development) or adverse exposures (e.g., pregnancy and birth complications, central nervous system diseases) are associated with an increased risk for schizophrenia. However, upper social class girls and clever schoolboys also have an increased risk to develop schizophrenia, contrasted to their peers. Individuals who subsequently develop schizophrenia follow a developmental trajectory that partly and subtly differs from that of the general population; this trajectory lacks flexibility and responsiveness compared to control subjects, at least in the early stages. We propose a descriptive, lifespan, multilevel systems model on the development and course of schizophrenia.

Key words: Schizophrenia, risk factors, developmental trajectory, multilevel systems model

Subtle developmental deviances in motor, cognitive, emotional, behavioural, and brain structural domains are often present in individuals who later develop psychosis. This strongly suggests that some aspects of causation are established before overt psychosis, and that these same factors impact adversely on various developmental trajectories (1-3). The Northern Finland 1966 Birth Cohort (NFBC 1966) aims to explore risk factors and developmental pathways to schizophrenia over the lifespan.

There are numerous proposed putative risk factors for schizophrenia (see 3,4 for reviews), but few prospective studies exist concerning the stability of developmental deviance and related phenotypic anomalies in schizophrenia. The NFBC 1966 has produced critical findings on the predictors of schizophrenic psychoses, e.g., unwanted pregnancy (5), obstetric complications (6), and delayed development at age 1 (7). Here we update these single risk factors up to the end of year 2001 or age 34. In particular, in this paper we explore whether deviation from the norm in either direction (i.e., either inferior or superior performance) could be a risk factor for schizophrenia.

METHODS

Within the NFBC 1966, we recruited 12,058 subjects born in 1966; 96% of all births in the region (1). In the follow-up at age 34, we used standard cohort approaches and a nested case-control design. We had 10,458 controls and 111 DSM-III-R schizophrenia cases in risk analyses. For each risk factor, crude and adjusted odds ratios are presented, along with population attributable risk (PAR) percentage, and variance explained. Total variance explained for the entire adjusted model is presented.

RESULTS

In Table 1 the significant risk factors within the NFBC 1966 by age 34 are presented. When adjusted for other variables, the rank order of risk factors changes substantially. Risk factors associated with relatively large crude odds ratio (e.g., perinatal brain damage) are associated with low PAR (e.g., 5%). Early developmental milestones related to standing, walking and potty training are associated with modest crude odds ratio, but relatively large PAR. When the risk factors are combined, only 9.1% of the variance can be explained. Not only "poor" performance is associated with elevated risk of schizophrenia: upper social class girls and clever schoolboys had an increased risk to develop schizophrenia, contrasted to their peers.

DISCUSSION

Compared to the general population, individuals who develop schizophrenia demonstrate subtle developmental deviances in motor, cognitive, emotional and behavioural domains. It is possible to identify risk factors for schizophrenia; however, they explain only a small proportion of variance and currently appear to have limited heuristic value. The results presented in recent reviews (4) are congruent with our findings and demonstrate similar developmental delays among preschizophrenic individuals.

Table 1 Most essential risk factors for schizophrenia in the Northern Finland 1966 Birth Cohort by age 34. Statistically significant risk factors are highlighted in bold

	Crude statistics				Adjusted odds ratio	
Risk factors	**OR**	**95% CI**	**R^2 %**	**PAR%**	**OR**	**95% CI**
Male gender	**1.8**	**1.2-2.7**	0.8	29	**1.8**	**1.1-2.8**
Parental psychosis*	**3.9**	**2.3-6.6**	1.5	11	**4.1**	**2.3-7.4**
Birth weight <2,500 g	**2.2**	**1.1-4.6**	0.3	4	1.4	0.6-3.4
Perinatal brain damage	**5.7**	**2.6-12.5**	1.1	5	**2.9**	**1.1-7.9**
Central nervous system infection	**2.9**	**1.1-8.0**	0.3	2	**3.7**	**1.3-10.6**
Unwanted pregnancy	**2.0**	**1.2-3.2**	0.6	10	**1.8**	**1.1-3.0**
Not in normal school grade	**4.4**	**2.7-7.1**	2.4	15	**4.4**	**2.5-7.7**
Late learning to stand (12 months or later)	**2.0**	**1.4-3.0**	1.1	24	1.4	0.8-2.4
Late learning to walk (12 months or later)	**1.9**	**1.2-3.0**	0.9	33	1.3	0.7-2.3
Potty trained at the age of 1 year (no)	**1.8**	**1.2-2.6**	0.7	19	1.5	1.0-2.3
Excellent school performance (in males)	**3.3**	**1.4-7.9**	0.7	7	**4.3**	**1.7-10.7**
Social class I (in females)	**2.4**	**1.0-5.8**	0.1	9	**4.5**	**1.6-13.4**

OR = odds ratio; CI = confidence interval; R^2% = how much variation is explained; PAR% = Population attributable risk percentage
* Information from Finnish Hospital Discharge Register, 1972-2000
Variance explained by the total model: R^2=9.1%

Usually, impaired performance (e.g., delayed motor or intellectual development) or adverse exposures (e.g., pregnancy and birth complications, central nervous system diseases) are associated with an increased risk for schizophrenia. Paradoxically, for some measures we found that the deviation from the norm in either direction was associated with an increased risk for schizophrenia. For example, within NFBC 1966, superior school performance was associated with increased risk for suicide in psychotic persons but with decreased risk among the non-psychotic population (interaction school performance x diagnosis: p = 0.01) (8).

Apart from the material presented in Table 1, research based on the NFBC has revealed other subtle deviances in the lifespan trajectory of individuals with schizophrenia compared to health members of the cohort. We were able to demonstrate that individuals with psychosis followed a developmental trajectory that partly and subtly differed from that of the general population. In preschizophrenic persons, the developmental pathway to adolescence appears stricter and lacks flexibility and responsiveness when contrasted to non-psychotic controls. There may be some continuity also in general population: infants within the NFBC 1966 who developed slightly more slowly (though still within the normal range of development) did less well at school and had a decreased chance of going on to higher education (9).

In schizophrenia, diagnostic accuracy may be limited and diagnostic transformations occur. Current diagnostic systems offer moderately good reliability among trained diagnosticians but not necessarily between scientists and clinicians (10). There are major problems concerning both validity issues and clinical practices, e.g., marked delay in diagnostics (11). In NFBC 1966, diagnostic disagreement or discordance (schizophrenia vs. no schizophrenia) between clinicians and researchers existed in 43% of cases, especially in cases with marginal symptomatology, minimal contacts to the treatment systems, late illness onset, good outcome and comorbidity (12).

Within the longitudinal data from the NFBC 1966, there is a different degree of developmental continuity or persistence of deviances in schizophrenia and the general population. The developmental continuity in the neuromotor area between 1 and 16 years among children who developed schizophrenia was significantly stronger (Spearman's r between 0.2 to 0.3) than non-psychotic controls (r between 0.05 to 0.1) (13). For cognition, within the NFBC 1966, those who had slight delays in developmental milestones during early life also performed worse on tests of cognitive function in adulthood. Whilst schizophrenia subjects developed slightly later and had poorer cognitive function in adulthood, the pattern of association between infant motor development and adult cognition was similar in schizophrenia and the general population (14). The cognitive pathway from infancy to adulthood was not qualitatively different in the schizophrenia group compared with the general population (15). There were quantitative differences (e.g., poorer performance seen in both infancy and adulthood in subjects with schizophrenia). These findings are consistent with the hypothesis that, in schizophrenia, mild infant motor developmental delay and adult cognitive deficits (at least in some domains) are age dependent manifestations of the same underlying neural process.

In Figure 1, we present a descriptive, multilevel lifespan model of the developmental pathway to schizophrenia and of the course of the illness. This descriptive model has its main focus on time-dependent (longitudinal), measurable epidemiologically identified properties. However, this model also has hierarchical multilevel features. The data from the NFBC 1966 provide tangible evidence of the

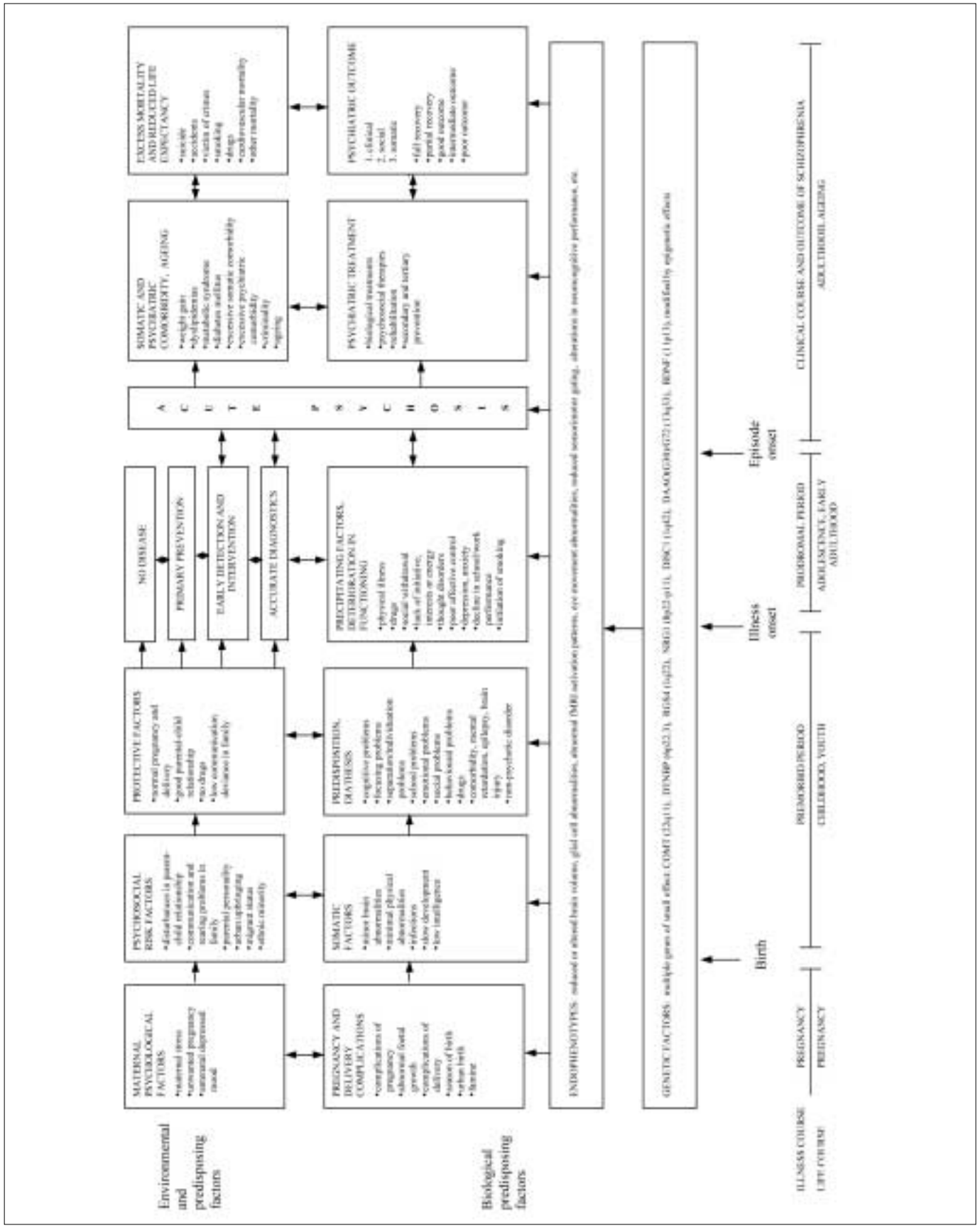

Figure 1 Descriptive life span and multilevel model of schizophrenia. Known aetiological and disease course components are presented. Hypothetical ideas on protective factors are not necessarily evidence-based.

complexity and subtlety of these pathways, but the variables now available only allow glimpses of potential genome and endophenotype levels. Current studies are examining candidate genes and endophenotypes and we hope to be able to use the developmental phenotypes and endophenotypes to sharpen gene association studies. Gottesman et al (16) have outlined an innovative model incorporating a dynamic developmental interplay among molecular genetic, environmental and epigenetic factors.

This model has value from several perspectives. It contains information on both the longitudinal, lifespan, dynamic, time-dependent and time-varying pathway, and the transversal, structural, multilevel, multidimensional, hierarchical pathway. Both these dimensions can illuminate hidden layers of complexity between genotype and disease. In the absence of an understanding of the complete systems, we only see the surface manifestations of the underlying processes. Descriptive phenotype-level risk factors and phenomena (e.g., age learned to walk, birth complications, unwanted pregnancy) are only partly heuristic and their explanatory and predictive power is modest.

In conclusion, individuals with psychosis follow a developmental trajectory that partly and subtly differs from that of the general population. The NFBC 1966 has allowed us the opportunity to observe glimpses of this complex process. It is necessary to develop theoretical frameworks of the developmental pathway of schizophrenia based on a more detailed, dynamic and multilevel approach, as proposed by modern systems theory and systems biology (17). Presently, it is not possible to construct a detailed model that captures all the features underlying the development of schizophrenia. We know too little about the inputs and mediating factors in the matrix of genes and environmental factors that gently guide development. However, we can conclude that the developmental trajectories in schizophrenia are different in subtle but informative ways compared to those of healthy individuals. For those who develop schizophrenia, the developmental pathways, at least in the early phase, seem "stricter". They may be less flexible and less able to buffer perturbations. These findings provide tantalizing glimpses into the component causes of schizophrenia, and emphasize the value of birth cohort studies.

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